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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/091,500	03/07/2002	Yusuke Amino	217637US0CONT	8895

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1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER

ZUCKER, PAUL A

ART UNIT	PAPER NUMBER
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1621

13

DATE MAILED: 12/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/091,500

Applicant(s)

AMINO ET AL.

Examiner

Paul A. Zucker

Art Unit

1621

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 September 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 23, 24 and 26-28 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 24 is/are allowed.
- 6) ☒ Claim(s) 23 and 26-28 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____. 6) ☐ Other: _____

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 25 September 2003 has been entered.

Current Status

2. This action is responsive to Applicants' amendment of 25 September 2003 in Paper No 12.
3. Receipt and entry of Applicants' amendment is acknowledged.
4. Applicant's cancellation of claims 1-22, 25 and 29-39 is acknowledged.
5. Claims 23, 24 and 26-28 are pending.
6. The rejection under 35 USC § 102(b) set forth in paragraph 11 of the previous Office Action in Paper No 10 is withdrawn in response to Applicants' amendment.
7. The rejections under 35 USC § 103(a) set forth in paragraphs 15, 17 and 19 of the previous Office Action in Paper No 10 are withdrawn in view of Applicants' cancellation of claims 1-22, 25 and 29-39.

New Rejections

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35

U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. Claims 23 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nofre et al (US 5,480,668 01-1996) in view of Claude et al (US 5,510,508 04-1996).

Instantly claimed is a method for the production of N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester comprising subjecting 3-(3-methoxy-4-hydroxyphenyl) propionaldehyde and Aspartame to reductive alkylation via hydrogenation in the presence of a catalyst followed by crystallization.

Nofre teaches (Column 8, Table 1, entries 18 and 19) the compounds N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester and its unsaturated counterpart. Nofre further teaches (Column 7, lines 24-51) a general process for its synthesis. Nofre teaches a process for reductive alkylation of

aspartame with the appropriate aldehyde (1.099 molar ratio aldehyde/aspartame) in methanol at room temperature for 24 hours. Nofre teaches removal of the reaction solvent (methanol), washing with aqueous HCl (to remove aspartame) and its replacement with ethanol/water as a recrystallization solvent (solvent substitution). Aspartame as well as other impurities, is removed via the disclosed crystallization.

The difference between the process taught by Nofre and the instant process is that Nofre teaches a process for reductive alkylation which employs sodium cyanoborohydride as a reductant while the instant application claims the use of a catalytic hydrogenation reaction.

Claude, however, teaches (Column 3, line 63- column 4, line 26) a reductive alkylation reaction between 3,3-dimethylbutyraldehyde and aspartame in methanol solution in the presence of platinum catalyst and hydrogen gas at 1 bar at room temperature.

Thus the instantly claimed process would have been obvious to one of ordinary skill in the art. The suggestion to combine is found in the nearly identical fields of invention. The motivation would have been to modify the general process for the synthesis of N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester taught by Nofre by replacing his conditions for reductive alkylation with those taught by Claude. There would have been a reasonable expectation for success based on the fact that one equivalent hydrogenation process replaces another to produce the instant process.

Examiner's Response to Applicants' Remarks With Regard to This Rejection

9. Applicants present several arguments with regard to this rejection. The Examiner responds to these below:

- a. Applicants argue that Nofre does not describe that the series of compounds set forth can be purified with the same or similar solvents as that used for the synthesis of N-[N-[3,3-dimethylbutyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester which is exemplified. The Examiner disagrees. In fact, Nofre expressly teaches (Column 7, lines 61-67) that similar procedures to that disclosed for the synthesis of N-[N-[3,3-dimethylbutyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester are employed to give the compounds of Table 1 which includes the compound N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester which is at issue in this application. In the absence of some indication to the contrary on the part of Nofre, one of ordinary skill in the art would understand that Nofre thus teaches that the compounds of Table 1 are both crystalline and obtainable in such form by the method disclosed for N-[N-[3,3-dimethylbutyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester
- b. Applicants make further arguments regarding inherency that are not germane to the present rejection since the polymorphic crystalline form is not a limitation of instant claims 23 and 26.

Applicant's arguments filed 25 September 2003 have been fully considered but they are not persuasive for the reasons indicated above.

10. Claims 27 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nofre et al (US 5,480,668 01-1996) in view of Claude et al (US 5,510,508 04-1996).

Instantly claimed are a sweetening agent or sweetener comprising N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester produced by a process comprising subjecting 3-(3-methoxy-4-hydroxyphenyl) propionaldehyde and Aspartame to reductive alkylation via hydrogenation in the presence of a catalyst followed by crystallization.

Nofre teaches (Column 8, Table 1, entries 18 and 19) the compounds N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester and its unsaturated counterpart. Nofre further teaches (Column 7, lines 24-51) a general process for its synthesis. Nofre teaches a process for reductive alkylation of aspartame with the appropriate aldehyde (1.099 molar ratio aldehyde/aspartame) in methanol at room temperature for 24 hours. Nofre teaches removal of the reaction solvent (methanol), washing with aqueous HCl (to remove aspartame) and its replacement with ethanol/water as a recrystallization solvent (solvent substitution). Aspartame as well as other impurities, is removed via the disclosed crystallization. Nofre further teaches (Column 10, lines 42-47, claims 6 and 7) the use of the compound of N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester as a sweetening agent in combination with carriers or bulking agents.

The difference between the process taught by Nofre and the instant process is that Nofre teaches a process for reductive alkylation which employs sodium cyanoborohydride as a reductant while the instant application claims the use of a catalytic hydrogenation reaction.

Claude, however, teaches (Column 3, line 63- column 4, line 26) a reductive alkylation reaction between 3,3-dimethylbutyraldehyde and aspartame in methanol solution in the presence of platinum catalyst and hydrogen gas at 1 bar at room temperature.

Thus the instantly claimed process would have been obvious to one of ordinary skill in the art. The suggestion to combine is found in the nearly identical fields of invention. The motivation would have been to modify the general process for the synthesis of N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester taught by Nofre by replacing his conditions for reductive alkylation with those taught by Claude. There would have been a reasonable expectation for success based on the fact that one equivalent hydrogenation process replaces another to produce the instant process.

11. Applicants reference their argument with regard to claim 23 that Nofre does not describe that the series of compounds set forth can be purified with the same or similar solvents as that used for the synthesis of N-[N-[3,3-dimethylbutyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester which is exemplified. The Examiner disagrees. In fact, Nofre expressly teaches (Column 7, lines 61-67) that similar

procedures to that disclosed for the synthesis of N-[N-[3,3-dimethylbutyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester are employed to give the compounds of Table 1 which includes the compound N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester at issue in this application. In the absence of some indication to the contrary on the part of Nofre, one of ordinary skill in the art would understand that Nofre thus teaches that the compounds of Table 1 are both crystalline and obtainable in such form by the method disclosed for N-[N-[3,3-dimethylbutyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester or by a modification of such method within the skill of one of ordinary skill in the art.

Applicant's arguments filed 25 September 2003 have been fully considered but they are not persuasive for the reasons indicated above.

Declaration

12. The declaration of Professor Jerry Atwood has been considered. The declaration under 37 CFR 1.132 filed 25 September 2003 is sufficient to overcome the rejection of claim 24 under 35 U.S.C. 102(b) as being anticipated by Nofre et al (US 5,480,668 01-1996). Professor Atwood's statement (Declaration, Page 4, first full paragraph) regarding the unpredictability of polymorphic forms and the requirement for the description of the precise conditions for the reproducible production of a particular polymorph was found persuasive. The instantly claimed polymorph is also, therefore, not obvious over the teachings of Nofre.

Allowable Subject Matter

13. Claim 24 is allowed. The following is a statement of reasons for the indication of allowable subject matter: Because of the unpredictability of polymorphic forms and therefore the requirement for precise conditions for the reproducible production of a particular polymorph, Nofre disclosure of N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester and generic teaching of its crystallization from aqueous/alcoholic solution neither anticipates nor fairly suggests the instantly claimed polymorph of the subject compound.

Conclusion

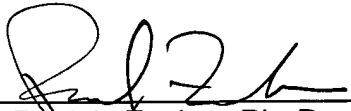
14. Claims 23, 24 and 26-28 are pending. Claims 23 and 26-28 are rejected. Claim 24 is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul A. Zucker whose telephone number is 703-306-0512. The examiner can normally be reached on Monday-Friday 7:00-3:30.

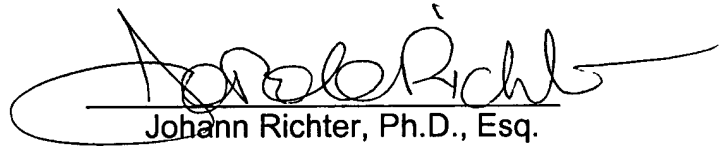
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on 703-308-4532. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.



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